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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,449	09/29/2005	Tatsuhiko Kodama	278547US0X PCT	2982

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/01/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/01/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/551,449	KODAMA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 12/28/05, 9/29/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

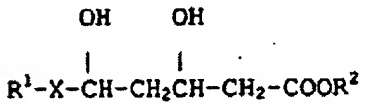
1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

2. Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

3. This application claims benefit to provisional application No. 60/463311, filed on 04/17/2003, in a language other than English. An English translation of the non-English language provisional application and a statement that the translation is accurate must be filed in provisional application No. 10/551449. See 37 CFR 1.78(a)(5). The English translation and statement that the translation is accurate required by 37 CFR 1.78(a)(5) is missing. Accordingly, applicant must supply 1) the missing English translation and statement in provisional application No. 60/463,311 and 2) in the present application, a confirmation that the translation and statement were filed in the provisional application. If 1) and 2) are not filed (or the benefit claim withdrawn by the filing of an amendment or Supplemental Application Data Sheet) prior to the expiration of the time period set in this Office action, the present application will be abandoned. See 37 CFR 1.78(a)(5)(iv).

For the purposes of prosecution the following is defined:

4. Page 4 of the specification teaches the formula (1):



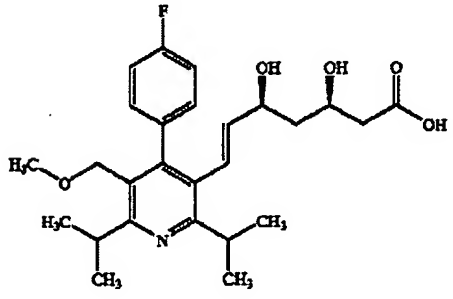
Page 9 of specification further teaches:

5. Compounds represented by the formula (1), their lactone derivatives and salts of these compounds and lactone derivatives, all of which are usable in the present invention, are known as HMG-COA reductase inhibitors useful as hyperlipidemia therapeutics.

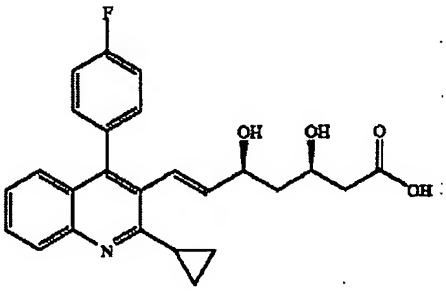
Thus for the purposes of prosecution, any HMG-CoA reductase inhibitor comprises the basic formula (1) as defined by applicant.

Storz (U.S. Patent No. 6,909,003) teaches the chemical structures of several well known statins:

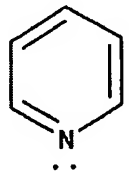
Cerivastatin



Pitavasatin



both structures have, at the very least a pyridyl group:



Pyridine. Milton Orchin. The Vocabulary and Concepts of Organic Chemistry *2Nd Ed.* Hoboken, N.J John Wiley & Sons, Inc. (US), 2005. pg 78.

Double Patenting

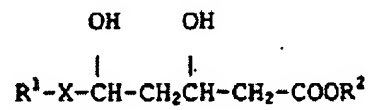
6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,011,930. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 of the instant application represent a genus over the

species claims 1-7 in U.S. Patent No. 5,011,930. Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

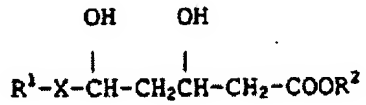


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

8. Claims 1-7 of US Patent No. 5,011,930 comprise HMG-CoA reductase inhibitors, and include embodiments including pitavastatin. The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

9. Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,284,953. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 of the instant application represent a genus over the species claim 1 in U.S. Patent No. 5,284,953. Instant claims 1-5 read on a compound capable of

inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

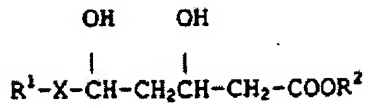


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

10. Claim 1 of US Patent No. 5,284,953 comprise HMG-CoA reductase inhibitors, and include embodiments including pitavastatin salt. The administration of the HMG-CoA reductase inhibitors including pitavastatin salt would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

11. Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,854,259. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 of the instant application represent a genus over the species claims 1-4 in U.S. Patent No. 5,854,259. Instant claims 1-5 read on a

compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

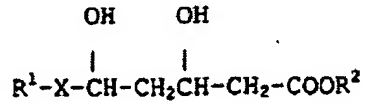


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

12. Claims 1-4 in U.S. Patent No. 5,854,259 comprise HMG-CoA reductase inhibitors, and include embodiments including pitavastatin. The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

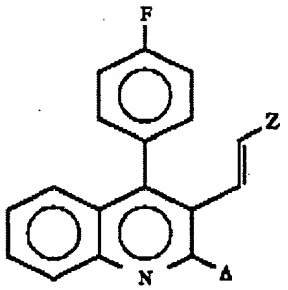
13. Claims 1-5, 9-13, are 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 5,856,336. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5, 9-13, are 17-21 of the instant application represent a genus over the species claims 1-2 in U.S. Patent No. 5,856,336.

Instant claims 1-5, 9-13, 17-21 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin, and methods of using pitavastatin.

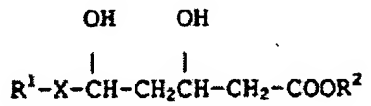
14. Patent 5,856,336 discloses the chemical structure for pitavastatin in claim 1:



15.  , and the methods for the use of pitavastatin in claim 2. The structure of the molecule of patent 5,856,336 inherently embodies the structural limitations of the instant claims, and methods of use the molecule are encompassed in claim 2 of patent 5,856,336. The administration of the pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known

inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

16. Claims 1-5, 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,872,130. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 9-13, 17-21 of the instant application represent a genus over the species claims 1-5 in U.S. Patent No. 5,872,130. Instant claims 1-5, 9-13, 17-21 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

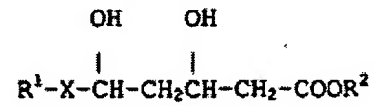


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin and methods of using the inhibitors.

17. Claims 1-5 of US Patent No. 5,872,130 comprise HMG-CoA reductase inhibitors, and include embodiments including pitavastatin. The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the

date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

18. Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,465,477. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 of the instant application represent a genus over the species claims 1-15 in U.S. Patent No. 6,465,477. Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

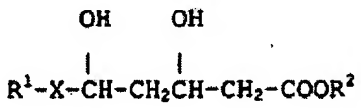


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

19. Claims 1-15 of US Patent No. 6,465,477 comprise a pharmaceutical composition comprising HMG-CoA reductase inhibitors, and include embodiments including pitavastatin. The administration of the pharmaceutical compositions comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid

inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

20. Claims 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 7,022,713. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9-13, and 17-21 of the instant application represent a genus over the species claims 1-2 in U.S. Patent No. 7,022,713. Instant claims 9-13, and 17-21 read on methods and uses of a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

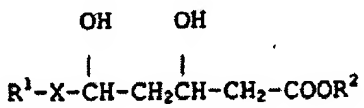


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

21. Claims 1-2 of U.S. Patent No. 7,022,713 comprise a method of treating a variety of diseases comprising using an effective amount of the HMG-CoA reductase inhibitor pitavastatin. The administration of the pharmaceutical compositions comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification,

applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

22. Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent Publication No. US 2004/0018235. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9-13, and 17-21 of the instant application represent a genus over the species claims 1-7 of U.S. Patent Publication No. US 2004/0018235. Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

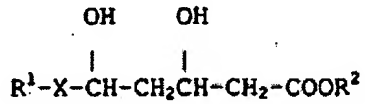


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

23. Claims 1-7 of U.S. Patent Publication No. US 2004/0018235 comprise a controlled release pharmaceutical composition comprising pitavastatin. The administration of the pharmaceutical composition pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of

the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. *This is a provisional double patenting rejection.*

24. Claims 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent Publication No. US 2003/0195167. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9-13, and 17-21 of the instant application represent a genus over the species claims 1-15 in U.S. Patent Publication No.US 2003/0195167. Instant claims 9-13, and 17-21 read on methods and uses of a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

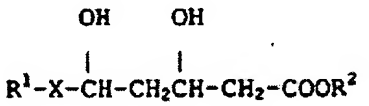


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase atorvastatin and pitavastatin.

25. Claims 1-15 of U.S. Patent Publication No. US 2003/0195167 comprise a method suppressing PTX3 gene expression by the administration of pitavastin and atorvastatin. The administration of the HMG-CoA reductase inhibitors including pitavastatin and atorvastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid

metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. *This is a provisional double patenting rejection.*

26. Claims 1-5, 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, and 7-13 of U.S. Patent Publication No. US 2005/0148626. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5, 9-13, and 17-21 of the instant application represent a genus over the species claims 1-2, and 7-13 in U.S. Patent Publication No. US 2005/0148626. Instant claims 1-5, 9-13, and 17-21 read on methods and uses of a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):

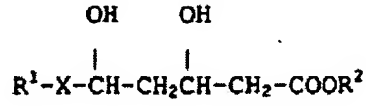


wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase atorvastatin and pitavastatin.

27. Claims 1-2, and 7-13 of U.S. Patent Publication No. US 2005/0148626 comprise a thrombomodulin expression promoter comprising the HMG-CoA reductase inhibitor pitavastatin and methods of treating a patient with the compound. The administration of

the HMG-CoA reductase inhibitors including pitavastatin and atorvastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. *This is a provisional double patenting rejection.*

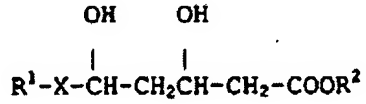
28. Claims 1-5 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-8 of U.S. Patent Publication No. US 2006/0111437. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 of the instant application represent a genus over the species claims 7-8 in U.S. Patent Publication No. US 2006/0111437. Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

29. Claims 7-8 of U.S. Patent Publication No. US 2006/0111437 comprise a therapeutic agent comprising the HMG-CoA reductase inhibitor pitavastin. The administration of the HMG-CoA reductase inhibitor pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. *This is a provisional double patenting rejection.*

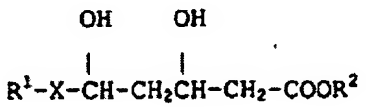
30. Claims 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent Publication No. US 2006/0217352. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9-13, and 17-21 of the instant application represent a genus over the species claims 1-17 in U.S. Patent Publication No. US 2006/0217352. Claims 9-13, and 17-21 read on methods and uses of a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

31. Claims 1-17 of U.S. Patent Publication No. US 2006/0217352 comprise a method for treating thrombosis by the administration of effective doses of pitavastin. The administration of the HMG-CoA reductase inhibitor pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. *This is a provisional double patenting rejection.*

32. Claims 1-5, 9-13, and 17-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9-17 of U.S. Patent Publication No. US 2006/0257474. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-5, 9-13, and 17-21 of the instant application represent a genus over the species claims 1-7, 9-17 in U.S. Patent Publication No. US 2006/0257474. Instant claims 1-5, 9-13, and 17-21 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

33. Claims 1-7, 9-17 of U.S. Patent Publication No. US 2006/0257474 comprise a therapeutic agent and pharmaceutical compositions comprising the HMG-CoA reductase inhibitor pitavastin and the administration of the compositions to a patient. The administration of the HMG-CoA reductase inhibitor pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. *This is a provisional double patenting rejection.*

Claim Rejections - 35 USC § 112

34. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35. Claims 2, 9, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

36. Claims 2, 9-16 and 18 recite the limitation "lactone derivative thereof." The phrase "lactone derivative thereof" is not defined in the specification. The phrase "derivative" implies a degree of change. Is this a change to a lactone? Or from a lactone? In what manner is there change? How much change is required for a non-lactone molecule to be a derivative of a lactone? How much change from a lactone molecule can occur before it is no longer derived from said lactone? A skilled artisan would be unable to determine the metes and bounds of the claimed invention.

37. Claims 10-16 provide for the use of promoters capable of promoting LKLF/KLF2 gene expression, wherein the promoter is a substance capable of inhibiting the mevalonic acid pathway, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

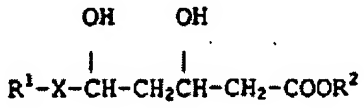
38. Claims 10-16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

39. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

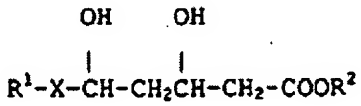
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

40. Claims 1-4, 6-7, 9-12, 14-15,17-20, and 22-23 are rejected under 35 U.S.C. 102(a) as being taught by Parmar et al (Statins Exert Endothelial Atheroprotective Effects via the Klf2 Transcription Factor. The Journal of Biological Chemistry, 2005. 280(29) 26714-26719). Claims 1-4, and 6-7 read on a compound that is capable of inhibiting the mevalonic acid metabolic pathway that promotes LKLF/KLF2 gene expression (claim 1). The compound is limited to formula (1) comprising:

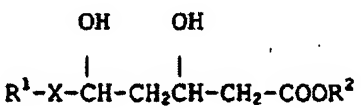


41. Wherein R^1 represents and organic group, X represents $-CH_2Ch_2-$ or $-CH=CH-$, and R^2 represents a hydrogen atom, alkyl group, or a lactone derivative thereof, or a salt (claim 2) and wherein formula (1) is limited to a variety of cyclic R groups including a pyridyl group (claim 3). The compound is limited to lovastatin, pravastatin, simvastatin,

fluvastatin, cerivastin, atorvastin, rosuvastatin, mevastatin or pitavastatin (claim 4) or a farnesyltransferase inhibitor (claim 6) or a geranyltransferase I inhibitor (claim 7). Claims 9-12, 14-15 read on the use of a compound that is capable of inhibiting the mevalonic acid metabolic pathway for promoting LKLF/KLF2 gene expression (claim 9). The compound is limited to formula (1) comprising:



42. Wherein R^1 represents and organic group, X represents $-CH_2Ch_2-$ or –CH=CH-, and R^2 represents a hydrogen atom, alkyl group, or a lactone derivative thereof, or a salt (claim 10) and wherein formula (1) is limited to a variety of cyclic R groups including a pyridyl group (claim 11). The compound is limited to lovastatin, pravastatin, simvastatin, fluvastatin, cerivastin, atorvastin, rosuvastatin, mevastatin or pitavastatin (claim 12) or a farnesyltransferase inhibitor (claim 14) or a geranyltransferase I inhibitor (claim 15). Claims 17-20, and 22-23 read on a method of promoting the expression of the LKLF/KLF2 gene by the administration of an effective amount of a substance capable of inhibiting the mevalonic acid metabolic pathway (claim 17). The substance is limited to formula (1) comprising:



43. Wherein R^1 represents and organic group, X represents $-CH_2Ch_2-$ or –CH=CH-, and R^2 represents a hydrogen atom, alkyl group, or a lactone derivative thereof, or a

salt (claim 18) and wherein formula (1) to a variety of cyclic R groups including a pyridyl group (claim 19). The substance is limited to lovastatin, pravastatin, simvastatin, fluvastatin, cerivastin, atorvastin, rosuvastatin, mevastatin or pitavastatin (claim 20) or a farnesyltransferase inhibitor (claim 22) or a geranyltransferase I inhibitor (claim 23).

44. According to the specification, any HMG-CoA reductase inhibitor fulfills the formula requirements of Formula (1) (see above).

45. Parmar et al teaches that statins (HMG-CoA reductase inhibitors), farnesyltransferase inhibitors and geranyltransferase I inhibitors are capable of upregulating KLF2 gene expression (see figure 1 A and B, and figure 2.) Parmar teaches the use of the HMG-CoA reductase inhibitors lovastatin, pravastatin and cerivastin, as well as the farnesyltransferase inhibitor FTI-277 and geranyltransferase I inhibitor GGTI-298 are all capable of increasing KLF2 expression (see materials and method section, page 26715 and also 26716). Parmer teaches that these HMG-CoA reductase inhibitors and the farnesyltransferase inhibitors and geranyltransferase I inhibitors are incubated with HUVEC cells to produce their effect, and measures KLF2 expression by RT-PCR.

46. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have

the capability of increasing KLF2 expression, and fulfill the requirements of claims 1-4, 6-7, 9-12, 14-15,17-20, and 22-23. Thus Parmer teaches the claimed invention.

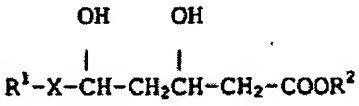
47. Claims 1-4, 8-12, 16-20, 24, are rejected under 35 U.S.C. 102(b) as being taught by Hausding et al (Inhibition of small G proteins of the Rho family by statins or *Clostridium difficile* toxin B enhances cytokine-mediated induction of NO synthase II. British Journal of Pharmacology, 2000. 131:553-561.) Claims 1-4, 8-12, 16-20, 24 read on mevalonic acid pathway inhibitors lovastatin and atorvastatin (claims 1-4, 9-12, 17-20) and glucosyltransferases (claims 8, 16, and 24) and methods of using them.

48. Hausding et al teaches a method of investigating the Ras and or Rho pathway includes statins and *Clostridium difficile* toxin B (TcdB) (a glucosyltransferase). He teaches that statins indirectly inhibit small G proteins by preventing their essential farnesylation (Ras) and/or geranylgeranlyation (Rho), wherein TcdB inactivates Rho-proteins directly (see abstract). He teaches that the use of the TcdB specifically inactivates the Rho proteins without affecting small G proteins of the Ras family (page 555, column II). Hausding teaches the use of statins lovastatin and atorvastatin and incubates the statins and the TcdB in human A549/8 and DLD-1 cells and murine NIH-3T3 cells (page 554). Hausding teaches that the cells are incubated with3-100uM of the statins, and .01 – 10 ng of Tcd – the incubations caused an increase in expression of NOS II mRNA, thereby being effective amounts.

49. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different than those used in the prior art. In fact, in the

examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression, and fulfill the requirements of claims 1-4, 6-7, 9-12, 14-15,17-20, and 22-23. Thus Parmer teaches the claimed invention.

50. Claims 1-5 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,011,930). Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

51. Fujikawa et al (US Patent No. 5,011,930) teaches HMG-CoA reductase inhibitors, and include embodiments including pitavastatin (see claims 1-7). The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have

the capability of increasing KLF2 expression. Thus Fujikawa teaches the claimed invention.

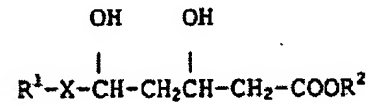
52. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

53. Claims 1-5 are directed to an invention not patentably distinct from claims 1-7 of commonly assigned US Patent No. 5,011,930. Specifically, instant claims 1-5 are a genus of the species claims 1-7 in US Patent No. 5,011,930, and are therefor encompassed by the subject matter in claims 1-7 of US Patent No. 5,011,930.

54. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 5,011,930, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

55. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

56. Claims 1-5 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Ohara et al (US Patent No. 5,284,953). Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

57. Ohara et al (US Patent No. 5,284,953) teaches HMG-CoA reductase inhibitors, and include embodiments including pitavastatin (see claim 1). The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Ohara teaches the claimed invention.

58. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

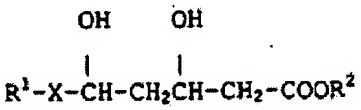
59. Claims 1-5 are directed to an invention not patentably distinct from claim 1 of commonly assigned US Patent No. 5,284,953. Specifically, instant claims 1-5 are a genus of the species claim 1 in US Patent No. 5,284,953, and are therefor encompassed by the subject matter in claim 1 of US Patent No. 5,284,953.

60. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 5,284,953, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

61. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

62. Claims 1-5 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,854,259). Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

63. Fujikawa et al (US Patent No. 5,854,259) teaches HMG-CoA reductase inhibitors, and include embodiments including pitavastatin (see claims 1-4). The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Fujikawa teaches the claimed invention.

64. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

65. Claims 1-5 are directed to an invention not patentably distinct from claims 1-4 of commonly assigned US Patent No. 5,854,259. Specifically, instant claims 1-5 are a genus of the species claims 1-4 in US Patent No. 5,854,259, and are therefor encompassed by the subject matter in claims 1-4 of US Patent No. 5,854,259.

66. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 5,854,259, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

67. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

68. Claims 1-5, 9-13, 17-21 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,856,336). Claims 1-5, 9-13, 17-21 read on the mevalonic acid pathway inhibitor pitavastatin and methods of using it.

69. Fujikawa et al (US Patent No. 5,856,336) teaches the HMG-CoA reductase inhibitor pitavastatin (claim 1) and methods of using pitavastatin for reducing hyperlipidemia, hyperlipoproteinemia, or atherosclerosis, which comprises administering an effective amount of pitavastatin (claim 2). Fujikawa teaches that the compound is administered to both HepG2 cells in vitro and Male Sprague-Dawley rats in vivo which resulted in a decrease in cholesterol biosynthesis (see Tests A-C, columns 12- 13).

70. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway HMG-CoA reductase inhibitor pitavastatin is different than that used in the prior art. In fact, the specification teaches in the examples 1-3, applicant merely incubates HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression, and fulfill the requirements of claims 1-5, 9-13, 17-21. Thus Fujikawa teaches the claimed invention.

71. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

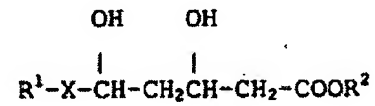
the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

72. Claims 1-5, 9-13, 17-21 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned US Patent No. 5,856,336. Specifically, instant claims 1-5, 9-13, 17-21 are a genus of the species claims 1-2 in US Patent No. 5,856,336, and are therefor encompassed by the subject matter in claims 1-2 of US Patent No. 5,856,336.

73. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 5,856,336, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

74. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

75. Claims 1-5 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Muramatsu et al (US Patent No. 6,465,477). Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin.

76. Muramatsu et al (US Patent No. 6,465,477) teaches HMG-CoA reductase inhibitors, and include embodiments including pitavastatin (see claims 1-15). The administration of the HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Muramatsu teaches the claimed invention.

77. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

78. Claims 1-5 are directed to an invention not patentably distinct from claims 1-5 of commonly assigned US Patent No. 6,465,477. Specifically, instant claims 1-5 are a genus of the species claims 1-15 in US Patent No. 6,465,477, and are therefor encompassed by the subject matter in claims 1-15 of US Patent No. 6,465,477.

79. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 6,465,477, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

80. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

81. Claims 9-13, 17-21 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Aoki et al (US Patent No. 7,022,713). Claims 9-13, 17-21 read on methods of using the mevalonic acid pathway inhibitor pitavastatin.

82. Aoki et al (US Patent No. 7,022,713) teaches a method of treating hypertriglyceridemia comprising using an effective amount of the HMG-CoA reductase inhibitor pitavastatin (see claims 1-2). The administration of the composition comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Aoki teaches the claimed invention.

83. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

84. Claims 9-13, 17-21 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned US Patent No. 7,022,713. Specifically, instant claims

9-13, 17-21 are a genus of the species claims 1-2 in US Patent No. 7,022,713, and are therefor encompassed by the subject matter in claims 1-2 of US Patent No. 7,022,713.

85. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 7,022,713, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

86. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

87. Claims 9-13, 17-21 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Morikawa et al (US Patent Publication No. US 2003/0195167). Claims 9-13, 17-21 read on the mevalonic acid pathway inhibitor pitavastatin and methods of using it.

88. Morikawa et al (US Patent Publication No. US 2003/0195167) teaches a method of suppressing expression of the PTX3 genes using pitavastatin, method of treating autoimmune disease and rheumatoid arthritis using pitavasatin (see claims 1-15).

89. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway HMG-CoA reductase inhibitor pitavastatin is different than that used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression, and fulfill the requirements of claims 9-13, 17-21. Thus Morikawa teaches the claimed invention.

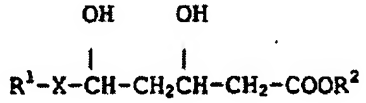
90. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

91. Claims 9-13, 17-21 are directed to an invention not patentably distinct from claims 1-15 of commonly assigned US Patent Publication No. US 2003/0195167. Specifically, instant claims 9-13, 17-21 are a genus of the species claims 1-15 in US Patent Publication No. US 2003/0195167, and are therefor encompassed by the subject matter in claims 1-15 of US Patent Publication No. US 2003/0195167.

92. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent Publication No. US 2003/0195167, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

93. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

94. Claims 1-5 are rejected under 35 U.S.C. 102(b/e) as being anticipated by Tanizawa et al (US Patent Publication No. US 2004/0018235) published 01/29/04. Instant claims 1-5 read on a compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the HMG-CoA reductase pitavastatin. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Tanizawa et al (US Patent Publication No. US 2004/0018235). Claims 1-5 read on the mevalonic acid pathway inhibitor pitavastatin.

95. Tanizawa et al (US Patent Publication No. US 2004/0018235) teaches a controlled release pharmaceutical composition comprising using an effective amount of the HMG-CoA reductase inhibitor pitavastatin for the treatment of hypercholesterolemia (see claims 1-7). The administration of the composition comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Tanizawa teaches the claimed invention.

96. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

97. Claims 1-5 are directed to an invention not patentably distinct from claims 1-7 of commonly assigned US Patent Publication No. US 2004/0018235. Specifically, instant claims 1-5 are a genus of the species claims 1-7 in US 2004/0018235, and are therefor encompassed by the subject matter in claims 1-7 of US Patent Publication No. US 2004/0018235.

98. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent Publication No. US 2004/0018235, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

99. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

100. Claims 1-5, 9-13, and 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Oida et al (US Patent Publication No US 2005/0148626) published

07/07/2005. Claims 1-5, 9-13, and 17-21 read on methods of using the mevalonic acid pathway inhibitor pitavastatin.

101. Oida et al (US Patent Publication No US 2005/0148626) teaches a method of treating a coagulation disorder, a patient suffereing from sepsis using pitavastatin comprising using an effective amount of the HMG-CoA reductase inhibitor pitavastatin (see claims 1-2, 7-13). The administration of the composition comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Oida teaches the claimed invention.

102. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

103. Claims 1-5, 9-13, and 17-21 are directed to an invention not patentably distinct from claims 1-2, 7-13 of commonly assigned US Patent Publication No. US

2005/0148626. Specifically, instant claims 1-5, 9-13 and 17-21 are a genus of the species claims 1-2, 7-13 in US Patent Publication No. US 2005/0148626, and are therefor encompassed by the subject matter in claims 1-2, 7-13 of US Patent Publication No US 2005/0148626.

104. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent Publication No. US 2005/0148626, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

105. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

106. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Aoki et al (US Patent Publication No US 2006/0111437) published 05/25/2006. Claims 1-5 read compositions comprising the mevalonic acid pathway inhibitor pitavastatin.

107. Aoki et al (US Patent Publication No US 2006/0111437) teaches a hypertriglyceridemia therapeutic agent composition comprising the HMG-CoA reductase inhibitor pitavastatin (see claims 7-8). The administration of the composition comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Aoki teaches the claimed invention.

108. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

109. Claims 1-5 are directed to an invention not patentably distinct from claims 7-8 of commonly assigned US Patent Publication No US 2006/0111437. Specifically, instant claims 1-5 are a genus of the species claims 7-8 in US Patent Publication No US 2006/0111437, and are therefor encompassed by the subject matter in claims 7-8 of US Patent Publication No US 2006/0111437.

110. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent Publication No US 2006/0111437, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

111. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

112. Claims 9-13, 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Yokoyanna et al (US Patent Publication No US 2006/0217352) published 07/28/2006. Claims 9-13, 17-21 read compositions and methods of using compositions comprising the mevalonic acid pathway inhibitor pitavastatin.

113. Yokoyanna et al (US Patent Publication No US 2006/0217352) teaches a method for treating thrombisis comprising the administration of the HMG-CoA reductase inhibitor pitavastatin (see claims 1-17). The administration of the composition

comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Yokoyanna teaches the claimed invention.

114. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

115. Claims 9-13, and 17-21 are directed to an invention not patentably distinct from claims 1-17 of commonly assigned US Patent Publication No US 2006/0217352. Specifically, instant claims 9-13, 17-21 are a genus of the species claims 1-17 in US Patent Publication No US 2006/0217352, and are therefor encompassed by the subject matter in claims 1-17 of US Patent Publication No US 2006/0217352.

116. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent Publication No US 2006/0217352,

discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

117. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

118. Claims 1-5, 9-13, 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Nakagawa et al (US Patent Publication No US 2006/025747) published 11/16/2006. Claims 1-5, 9-13, 17-21 read compositions and methods of using compositions comprising the mevalonic acid pathway inhibitor pitavastatin.

119. Nakagawa et al (US Patent Publication No US 2006/025747) teaches a anti-thrombotic therapeutic agent composition comprising the HMG-CoA reductase inhibitor pitavastatin and methods of treating a glomerular disease using the anti-thrombotic therapeutic agent comprising pitavastatin (see claims 1-7, 9-17). The administration of the composition comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no

teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression. Thus Nakagawa teaches the claimed invention.

120. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

121. Claims 1-5, 9-13, and 17-21 are directed to an invention not patentably distinct from claims 1-7, 9-17 of commonly assigned US Patent Publication No US 2006/025747. Specifically, instant claims 1-5, 9-13, 17-21 are a genus of the species claims 1-7, 9-17 in US Patent Publication No US 2006/025747, and are therefor encompassed by the subject matter in claims 1-7, 9-17 of US Patent Publication No US 2006/025747.

122. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent Publication No US 2006/025747,

discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

123. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

124. Claims 1, 6-7, 9, 14-15, 17, and 22-23 are rejected under 35 U.S.C. 102(b) as being taught by Lerner et al (Disruption of Oncogenic K-Ras4B Processing and Signaling by a Potent Geranylgeranyltransferase I Inhibitor. The Journal of Biological Chemicatry, 1995. 270(45):26770-26773.) Claims 1, 6-7, 9, 14-15, 17, and 22-23 read on mevalonic acid pathway farnesyltransferase inhibitors and geranyltransferase I inhibitors and methods of using them.

125. Lerner teaches several farnesyltransferase inhibitors and Geranylgeranyltransferase I inhibitors and methods of using them (see abstract). Lerner specifically teaches the incubation of the farnesyltransferase inhibitors FTI-276 and FTI-277, and the Geranylgeranyltransferase I inhibitors GGTI-287 and GGTI-286

on human Burkitt lymphoma cells in culture and measures their effect on the inhibition of GGTase I and FTase (see Table I, and experimental procedures section, page 26771).

126. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway farnesyltransferase inhibitors and geranyltransferase I inhibitors are different than those used in the prior art. In fact, the specification teaches in the examples 1-3, applicant merely incubates HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression, and fulfill the requirements of claims 1, 6-7, 9, 14-15, 17, and 22-23. Thus Lerner teaches the claimed invention.

Claim Rejections - 35 USC § 103

127. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

128. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

129. Claims 5, 13, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parmar et al (Statins Exert Endothelial Atheroprotective Effects via the Klf2 Transcription Factor. The Journal of Biological Chemistry, 2005. 280(29) 26714-26719). as applied to claims 1, 9, and 17 above, and further in view of Maejima et al (Effect of pitavastatin on apolipoprotein A-I production in HepG2 cell. Biochemical and Biophysical Research Communications, 2004. 324:835-839). Claims 5, 13, and 21 read on a compound that is capable of inhibiting the mevalonic acid metabolic pathway that promotes LKLF/KLF2 gene expression wherein the compound or pitavastatin (claim 5) and the use of pitavastatin to increase LKLf/KLF2 expression (claim 13) and a method of increasing LKLF/LKF2 expression by administering an effective amount of pitavastatin (claim 21).

130. Parmar et al teaches that statins (HMG-CoA reductase inhibitors), farnesyltransferase inhibitors and geranyltransferase I inhibitors are capable of up-regulating KLF2 gene expression (see figure 1 A and B, and figure 2.) Parmar teaches the use of the statins lovastatin, pravastatin and cerivastin, as well as the farnesyltransferase inhibitor FTI-277 and geranyltransferase I inhibitor GGTI-298 (see materials and method section, page 26715 and also 26716). Parmer teaches that these statins and inhibitors are incubated with HUVEC cells to produce their effect, and

measures KLF2 expression by RT-PCR. Parmer further teaches that the downstream pathway of the HMG-CoA pathway that is inhibited by statins include geranylgeranlyated proteins, such as Rho and Rac. Parmer teaches that KLF2 upregulation may be involved with the lipid lowering effects of statins (see abstract), and have an "atheroprotective effect" (page 26714 column II, last paragraph and page 26718 column II). Parmer does not teach the use of pitavastin.

131. Maejima et al teaches that HMG-CoA reductase inhibitors are capable of upregulating the expression of ApoA-1 in human cells (see abstract). Maejima uses the statins pitavastatin, simvastatin and atorvastatin, each of which showed an increase in ApoA-1 expression (see figure 2). Maejima teaches that pitavastatin is a new generation of statin that has more potent effects on hyperlipidemia (see page 835, column II). Maejima teaches that pitavastatin exerts a higher degree of ApoA-1 expression compared to simvastatin and atorvastatin (see figure 2 and page 837, column II)). Maejima further shows that pitavastatin is not only capable of upregulating ApoA-1 levels but also ABA1 mRNA (see figure 3 and page 836, Column II), and LXRα RNA all genes with lipid lowering capabilities (page 839, column I).

132. A skilled artisan would have been motivated to combine the teaching of Parmer on methods of using mevalonic acid pathway inhibitors such as HMG-CoA reductase inhibitors for the induction of KLF2 expression further with the teaching of Maejima on a new generation HMG-CoA reductase inhibitor, pitavastatin, that is capable of increasing the expression of multiple genes involved in treatment of hyperlipidemia that is more potent than older statins because the use of pitavastatin in Parmer's experiments would

likely increase the KLF2 expression to a greater degree than the older generation statins used in Parmer's experiments. It would have been obvious to the skilled artisan to combine the teaching of Parmer on the expression of KLF2 using various HMG-CoA reductase inhibitors with the teaching of Maejima on the increased potency of a new generation statin on the expression of genes linked to lipid lowering and atheroprotective genes in an attempt to elucidate the role the new generation statins had on the expression of KLF2. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

133. Claims 8, 16, and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Parmar et al (Statins Exert Endothelial Atheroprotective Effects via the Klf2 Transcription Factor. The Journal of Biological Chemistry, 2005. 280(29) 26714-26719). as applied to claims 1, 9, and 17 above, and further in view of Hausding et al (Inhibition of small G proteins of the Rho family by statins or *Clostridium difficile* toxin B enhances cytokine-mediated induction of NO synthase II. British Journal of Pharmacology, 2000. 131:553-561.) Claims 8, 16, and 24 read on a compound that is capable of inhibiting the mevalonic acid metabolic pathway that promotes LKLF/KLF2 gene expression wherein the compound is a glucosyltransferase (claim 8) and the use of a glucosyltransferase to increase LKLf/KLF2 expression (claim 16) and a method of increasing LKLF/LKF2 expression by administering an effective amount of a glucosyltransferase (claim 24).

134. Parmar et al teaches that statins (HMG-CoA reductase inhibitors), farnesyltransferase inhibitors and geranyltransferase I inhibitors are capable of up-regulating KLF2 gene expression (see figure 1 A and B, and figure 2.) Parmar teaches the use of the statins lovastatin, pravastatin and cerivastin, as well as the farnesyltransferase inhibitor FTI-277 and geranyltransferase I inhibitor GGTI-298 (see materials and method section, page 26715 and also 26716). Parmer teaches that these statins and inhibitors are incubated with HUVEC cells to produce their effect, and measures KLF2 expression by RT-PCR. Parmer further teaches that the downstream pathway of the HMG-CoA pathway that is inhibited by statins include geranylgeranlyated proteins, such as Rho and Rac. Parmer further teaches that the inhibitor GGTI-298 was specifically used because it is an inhibitor of geranylgeranly transferases, which are immediately upstream of the geranylgeranyated proteins (see page 2676, Figure 2A, and page 26716, last paragraph, column 1 bridging to column 2). Parmer does not teach the use of a glucosyltransferase as a compound capable of increasing KLF2 gene expression.

135. Hausding et al teaches a method of investigating the Ras and or Rho pathway includes statins and *Clostridium difficile* toxin B (TcdB) (a glusosyltransferase). He teaches that statins indirectly inhibit small G protein by preventing their essential farnesylation (Ras) and/or geranylgeranlyation (Rho), wherein TcdB inactivates Rho-proteins directly (see abstract). He teaches that the use of the TcdB specifically inactivates the Rho proteins without affecting small G proteins of the Ras family (page 555, column II).

136. A skilled artisan would have been motivated to combine the teaching of Parmer on methods of using mevalonic acid pathway inhibitors such as statins for the induction of KLF2 expression further with the teaching of Hausding, on the glusosyltransferase and statins can inhibit the mevalonic acid pathway, because TcdB inhibits the mevalonic pathway further downstream and is more specific for Rho proteins. while not affecting Ras proteins, because inhibiting the mevalonic pathway further downstream than statins will aid in the elucidation of the role that KLF2 plays in vascular functions. It would have been obvious to the skilled artisan to investigate the pathway in which KLF2 is involved in the mevalonic acid pathway and how HMG-CoA reductase inhibitors exert their effect on the KLF2 gene expression by trying to further delineate the pathway regulation using a variety of inhibitors. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

137. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kam/02/01/07

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PRIMARY EXAMINER